Substance use, medication adherence and outcome one year following a first episode of psychosis

ABSTRACT

Both substance use and poor medication adherence are associated with poor outcome in psychosis. To clarify the contributions of substance use and poor medication adherence to poor outcome in the year following a first episode of psychosis, 205 patients were evaluated for use of tobacco, alcohol, cannabis and stimulants at their psychosis onset, and in a 1-year follow-up. Data on medication adherence and symptom remission were also collected. Patients had high rates of overall substance use before (37-65%) and after psychosis onset (45-66%). 44% showed poor medication adherence and 55% did not reach remission from psychosis. Nicotine dependence and cannabis use after psychosis onset significantly predicted both poor medication adherence and non-remission, and poor medication adherence mediated the effects of these substances on non-remission. In conclusion, medication adherence lies on the causal pathway between nicotine dependence and cannabis on the one hand and non-remission on the other.

Keywords: First Episode Psychosis, Substance use, Cannabis use, Nicotine dependence, Medication adherence, Remission

1. INTRODUCTION

A number of studies have evaluated the impact that poor adherence to antipsychotic medication has on quality of life and hospitalizations in patients with psychosis (Gray et al., 2002; King et al., 2014, Park et al., 2014). Thus, poor medication adherence in patients following the first episode of psychosis (FEP) is associated with more frequent readmissions (Caseiro et al., 2012; Verdoux et al., 2000), and a greater risk of relapse (Kahn et al., 2008; Malla et al., 2006; Novak-Grubic and Tavcar, 2002).

Rates of poor adherence in FEP studies have been reported to range up to 71% (Hill et al., 2010; Levy et al., 2012; Miller et al., 2011). Use of substances, including cannabis and alcohol, has been found in several studies to be associated with poor medication adherence (Faridi et al., 2012; Hill et al., 2010; Lambert et al., 2010; Miller et al., 2009), as have a number of other demographic and clinical factors (Hill et al., 2010; Lambert et al., 2010). Furthermore, comorbid substance use has emerged as one of the greatest obstacles to the effective treatment of persons with psychosis; substance use is a risk factor for both poor medication adherence and dropout from treatment. Moreover, some studies suggest a dose-response relationship between severity of substance use and medication adherence rates (Dixon, 1999; Miller et al., 2009; Wade et al., 2007).

Two major limitations of the published data on substance use disorder and poor medication adherence are the small sample size of most studies and the narrow focus, usually on use of only one substance. In addition, the relation of poor adherence to tobacco smoking has not to date been investigated. This is important given that tobacco smoking is highly prevalent among psychotic patients, and there have been recent suggestions that tobacco smoking may be a risk factor for both onset (Gurillo et al., 2015) and outcome (Krishnadas et al., 2012) of psychosis.

In a one year follow-up of first episode psychosis patients, we obtained detailed information on the most commonly used substances among psychiatric patients, including tobacco, alcohol, cannabis and stimulants (such as amphetamines) both at baseline and during their subsequent clinical contact. Therefore the strength of our study is the ability to address the following hypotheses: 1. substance use following illness onset (tobacco, alcohol, cannabis and other stimulants) impairs medication adherence; 2. Substance use is associated with poor outcome at 1 year follow-up, and poor medication adherence mediates this effect.

2. MATERIALS AND METHODS

2.1. Study design and sample

Participants were recruited as part of the Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) and the Physical Health and Substance Use Measures (PUMP) studies carried out at the Institute of Psychiatry, Psychology and Neuroscience, London (Di Forti et al., 2009). All patients presenting to the Adult Psychiatric services (18 years<age<65 years) of the South London and Maudsley NHS Foundation Trust between December 2005 and October 2010 with their first episode of psychosis (FEP) who gave consent, were recruited into the study. Eligibility was determined through examination of the clinical notes of new admissions and consultation with clinical teams, and then validated by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (WHO, 1992). Inclusion criteria required that patients had 7 or more consecutive days of psychotic symptom(s) and were presenting to the psychiatric services for the first time with psychosis. Patients with an IQ<70, poor English fluency, and with a known or suspected organic cause for psychosis were excluded.

The data presented here are based on the subset of the whole GAP/PUMP sample (N = 205/461, 44%) on whom we were able to complete follow-up assessments for the year after the first contact with psychiatric services for psychotic disorder, and obtain satisfactory data on substance use and medication adherence. The most common reasons for attrition during the follow-up period were disengagement from clinical team after first hospitalization/contact with mental health services (N = 62, 13.4%) or insufficient/unavailable clinical information on the entire follow-up period because of disengagement from mental health services at some point during the one year follow-up period (N = 137, 29.7%). Other reasons for drop out included: a) left the UK (N

= 16, 3.5%) or transferred to other mental health services within the UK (N = 10, 2.2%); b) death (non-suicide) (N = 11, 2.4%) or suicide (N = 3, 0.7%). Moreover, a small proportion of patients (N =17, 3.7%) were excluded from the study because they were found to have already been treated with antipsychotics before enrolment in the study.

2.2. Baseline assessments

2.2.1. Clinical and socio-demographic measures

Baseline information about age, gender, self-reported ethnicity, relationship status, employment status and level of education was collected using the Medical Research Council Social Scale (MRCSS; Mallett et al., 2002). Diagnosis was made according to DSM-IV/ICD-10 criteria using the Operational Criteria OPCRIT (McGuffin et al., 1991) based on both the clinical notes and the data collected with the SCAN (WHO, 1992) in the month following the first contact with psychiatric services for psychosis. All diagnoses were made by qualified psychiatrists and clinical researchers, who attended training and OPCRIT intra-class correlation assessment ($0.70 \leq$ Cronbach's $\alpha \leq 1$). Diagnoses were combined in two main categorical groups: 1. non-affective psychosis (ICD10 codes: F20-F29; WHO, 1992) and 2. affective psychosis (ICD 10 codes: F30-F33; WHO, 1992).

2.2.2. Substance use evaluation

Subjects who reported tobacco use were interviewed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991). This questionnaire is a standard instrument for assessing the intensity of physical addiction to nicotine in the general population and provides an ordinal measure of nicotine dependence related to cigarette smoking. It contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence. In the FTND, yes/no items are scored from 0 to 1 and multiple-choice items are scored from 0 to 3. The items are summed to yield a total score of 0-10. The higher the total Fagerström score, the more

intense is the patient's physical dependence on nicotine. Subjects with FTND scores ≥5 were classified as nicotine-dependent.

Similarly, participants who reported alcohol use were interviewed using the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1989). This questionnaire is a reliable and simple screening tool which is sensitive to early detection of risky and high risk (or hazardous and harmful) drinking. It has ten questions on alcohol consumption (1 to 3), dependence (4 to 6), and the consequences or problems related to drinking (7 to 10). Questions 1 to 8 are scored on a five-point scale from 0, 1, 2, 3, and 4. Questions 9 and 10 are scored on a three-point scale from 0, 2 and 4. The maximum total score is 40. Evidence from studies determining the validity and reliability of the AUDIT for detecting problem drinking in a population of FEP indicate that the AUDIT functions best with a cut-off score of 10 (sensitivity, 85%; specificity, 91%; Cassidy et al., 2008). Subjects with AUDIT scores ≥10 were classified as problem drinkers in this study.

FEP patients were administered the Cannabis Experience Questionnaire modified version (CEQ_{MV}; Colizzi et al., 2015a; Colizzi et al., 2015b; Di Forti et al., 2012) at baseline. This questionnaire provides information on lifetime use of cannabis, tobacco, stimulants and other drugs at enrollment. The CEQmv allows detailed assessment of patterns of cannabis and as well as use of other illicit drugs including stimulants, including age at first use, frequency and duration of use, and the specific type of cannabis used.

2.3. Case-tracing procedure

The one-year follow-up period was taken as the date of first contact with mental health services of the South London and Maudsley Mental Health NHS Foundation Trust (SLAM) for psychosis to the date exactly one year later using the clinical records held on the SLAM electronic Patient Journey System (ePJS). All of the following measures were completed by a researcher retrospectively from the electronic mental health records system (ePJS of SLAM).

2.4. Follow-up assessments

Clinical, socio-demographic and substance use data were collected with the Follow-up Psychiatric and Personal History Schedule (FU-PPHS). The PPHS is a schedule to record information about mental state, general behavior, substance use, events and personal history of the patient during a follow-up period; information can be obtained from patients, informants, case notes and other records (Janca and Chandrashekar, 1995). Researchers involved in rating the PPHS at follow-up achieved an excellent intra-class correlation (> 0.90) on all PPHS items when duplicate ratings were compared.

2.4.1. Clinical assessment: medication adherence and remission

Information on medication adherence and remission during the one year follow-up was extracted from the PPHS (Janca and Chandrashekar, 1995). In the PPHS, poor adherence is defined as: 1=lapses of 3 or more days more than once; 2= not taking any prescribed medication. Remission is operationally defined as: absence of positive, negative or disorganized symptoms for at least 30 days.

2.4.2. Substance use evaluation

Substance use over the one year follow-up was scored using FTND (Heatherton et al., 1991), AUDIT (Babor et al., 1989), and CEQ_{MV} (Colizzi et al., 2015a; Colizzi et al., 2015b; Di Forti et al., 2012), in the same manner as for baseline.

2.5. Ethical approval

This study was granted ethical approval by the South London and Maudsley and Institute of Psychiatry Local Research Ethics Committee. All patients included in the study gave informed written consent to be assessed at baseline, to be re-contacted at follow-up; they gave permission to access their clinical records and the publication of data originating from the study.

2.6. Data Analysis

ANOVAs and χ^2 were used to evaluate the relation between sample characteristics [socio-demographic measures (age, gender, ethnicity, relation status, employment status, and level of education) and diagnosis (affective/non-affective psychosis)] and substance use [yes/no; nicotine dependence, problem drinking, cannabis use, and stimulant use]. Also ANOVAs and χ^2 were used to analyze the association between sample characteristics and medication adherence during the one year follow-up.

According to Byron and Kenny (1986), evidence for mediation requires the satisfaction of four criteria. The first two criteria require that a significant association between the independent variable and the mediator (path a) and the independent variable and the outcome variable (path c) be established. In order to evaluate these criteria, multivariable logistic regressions, with nicotine dependence, problem drinking, cannabis use, and stimulant use (yes/no) as independent variables, were used to test the effect of each substance before psychosis onset (premorbid use) on medication adherence (path a) and remission (path c) during the one year follow-up after adjusting for socio-demographic measures (age, gender, ethnicity, relation status, employment status, and level of education). Similar analyses were performed to test the associations between each substance use after psychosis onset (use in the one year follow-up period) and medication adherence (path a) as well as between each substance use after psychosis onset and remission (path c).

The third criterion requires that the mediator predicts the dependent variable even when the independent variable is controlled for (path b). In order to evaluate this criterion, logistic regressions were used to test the effect of medication adherence on remission (path b) during the one year follow-up after adjusting for socio-demographic measures. The same analysis was performed again after adjusting also for substance use. The final criterion requires assessing the degree of attenuation between the independent and outcome variables after adjustment for the mediator (path c'). A complete mediating effect occurs when the association between the independent and the dependent variable is eliminated when the mediator is controlled for. For this criterion, multivariable logistic regressions, with nicotine dependence, problem drinking, cannabis

use, and stimulant use (yes/no) as independent variables, were used to test the effect of each substance on remission during the one year follow-up after adjusting for socio-demographic measures and medication adherence. After standardizing each regression coefficient (multiplied by the standard deviation of the predictor variable and divided by the standard deviation of the outcome variable), the decomposition has been computed. The Sobel test was utilized to evaluate the statistical significance of the mediation effect (Sobel and Leinhardt, 1982).

3. RESULTS

3.1. Socio-demographic characteristics

Out of 205 FEP patients on whom we obtained complete data at 1 year, 63.4% were male. There were no significant differences between those in whom complete data were obtained (N = 205) and those in whom it was not (N = 256) in terms of gender, age at first contact, ethnicity, relationship status, employment status, education level and diagnosis (all $p > 0.1$). The average age at first contact with psychiatric services for psychotic disorder was 29.6 years (± SD, ± 9.9 years). 35% of the FEP were White, 43% Black African/Caribbean and 22% Asian/other. The majority of the patients were single (73.7%) and unemployed (63.9%), and had completed only secondary education (60.5%). Using the OPCRIT diagnostic assessment, 75.6% of the patients satisfied ICD-10 criteria for non-affective psychosis (F20-F29; Table 1).

3.2. Substance use, medication adherence, and remission

At baseline 53.2% reported premorbid nicotine dependence, 40.5% premorbid problem drinking, 65.4% premorbid cannabis use, and 36.6% premorbid stimulant use (Table 2). Neither socio-demographic characteristics nor diagnosis (non-affective vs. affective psychosis) was associated with any type of substance use at baseline (all $p > 0.1$).

The 1 year follow-up evaluation revealed that 59.5% of the FEP were dependent on nicotine, 42% problem drinkers, 66.3% were cannabis users, and 44.9% stimulant users (Table 2). Neither socio-demographic characteristics nor diagnostic categories were associated with any type of substance use during the follow-up (all $p > 0.1$).

43.9% of the patients adhered poorly to their pharmacological treatment at some point during the first year of following their first episode of psychosis (at least two lapses of 3 or more days; Table 2). Neither socio-demographic characteristics nor diagnosis categories were associated with medication adherence during the follow-up period (all $p > 0.1$). More than 50% of the patients

failed to satisfy PPHS criteria for remission (Table 2). Neither socio-demographic characteristics nor diagnostic categories were associated with remission status (all $p > 0.1$).

3.3. Mediation analyses

No single substance use before the first episode of psychosis reached significance for an association with medication adherence during the follow-up (path a). Similarly, substance use before the psychosis onset was not associated with remission status at follow-up (path c). Therefore, the mediation analysis was terminated.

Substance use in the year after psychosis onset was associated with increased probability of poor medication adherence during the follow-up (path a). In particular, the analysis showed significant main effects of nicotine dependence (OR=2.18), cannabis use (OR=2.86), and stimulant use (OR=2.63) on the odds of being non adherent to treatment. In contrast, the OR failed to reach significance for an association between problem drinking and poor medication adherence (Table 3).

Substance use in the first year after psychosis onset was associated with increased probability of non-remission during the one year follow-up (path c). In particular, the analysis showed significant main effects of nicotine dependence (OR=2.13) and cannabis use (OR=2.60) on probability of not achieving remission. In contrast, the ORs failed to reach significance for an association between problem drinking and non-remission as well as between stimulant use and non-remission (Table 3).

Medication adherence significantly predicted remission during the one year follow-up (path b). In particular, patients with poor medication adherence showed a six-fold increased probability of non-remission of their psychosis when compared with patients with good medication adherence (Table 4). When substance use in the one year follow-up period was added in to this model, the association between medication adherence and remission was still significant (Table 4).

Following Baron and Kenny's approach to mediation, the first three criteria were satisfied only for nicotine dependence and cannabis use post onset. Therefore, the mediation analysis was

terminated for problem drinking and stimulant use. In order to test for the final criterion, the associations between nicotine dependence after psychosis onset and non-remission as well as between cannabis use and non-remission were adjusted for medication adherence (path c'). When medication adherence was added in to the model, even if increased, the ORs failed to reach significance (Table 3). Sobel tests for mediation showed that medication adherence was a significant mediator of the relationship between nicotine dependence and remission ($z = 2.02$, $p = .04$; Figure 1) as well as that between cannabis use and remission ($z = 2.12$, $p = .03$; Figure 1).

4. DISCUSSION

To our knowledge, this is the first study to systematically examine the association between use of the most common substances before and after psychosis onset, and clinical outcome over a one-year period in patients suffering their first episode of psychosis. The results indicate that both nicotine dependence and use of cannabis in the first year after psychosis onset affect medication adherence; furthermore, poor medication adherence is a strong predictor of non-remission. Finally, nicotine dependence and cannabis use in the first year after psychosis onset are associated with increased probability of non-remission during the one year follow-up, and medication adherence mediates these effects.

Our sample was characterized by high rates of substance use, both at time of the diagnosis and during the one year follow-up. The data are consistent with the literature, even if the prevalence of substance use we found is higher because we included any kind of use and not only categorically defined substance use disorders (Addington and Addington , 2007; Myles et al., 2012; Van Mastrigt et al., 2004). As in many previous studies (Coldham et al., 2002; Levy et al., 2012; Miller et al., 2011; Novak-Grubic and Tavcar, 2002; Verdoux et al., 2000), more than 40% of patients recruited showed poor adherence to their pharmacological treatment during the one year follow-up, but contrary to the published literature, this was not predicted by socio-demographic characteristics (Cotton et al., 2009; Perkins et al., 2008). Our findings are however in line with the previous literature (Alvarez-Jimenez et al., 2012) in showing an increased risk of non-remission due to poor medication adherence.

Our study evaluated the impact of substance use, both premorbidly and after psychosis onset, on medication adherence. Our findings indicate that premorbid substance use does not affect medication adherence during the one year follow-up. However, substance use during the year after psychosis onset significantly predicted poor medication adherence at follow-up. Lastly we clearly showed that substance use increases the risk of non-remission (Alvarez-Jimenez et al., 2012), with a

more than 2-fold increased likelihood of not achieving remission for nicotine dependent and cannabis using patients. These findings are novel in demonstrating that this association is mediated by poor medication adherence, implying that medication adherence lies on the causal pathway between substance use and non-remission.

Although nicotine dependence appears to be a risk factor for psychosis (Gurillo et al., 2015) and a predictor of worse clinical and social outcome in psychosis patients (Krishnadas et al., 2012), why this should be is still unclear (Gurillo et al., 2015; Krishnadas et al. 2012). One possibility is that chronic nicotine use dysregulated dopamine signaling (Brody et al., 2010). Our results indicate a role for medication adherence in the association between nicotine dependence and non-remission. Research suggests that certain personality factors may be involved in tobacco use and dependence, such as low conscientiousness and high levels of neuroticism (Zvolensky et al., 2015). One might therefore hypothesize that these personal characteristics make nicotine dependent patients less likely to adhere to medication.

Cannabis use has been consistently indicated as a risk factor for schizophrenia (Di Forti et al., 2009), and a review has indicated relapse and poor medication adherence as the two most relevant clinical outcomes affected by cannabis use in psychosis (Zammit et al., 2008). Our results clarify the nature of this relationship, suggesting a mediation effect of medication adherence in the association between cannabis use and non-remission. Several studies offer a possible neurobiological explanation for the increased non-adherence in cannabis users. Chronic cannabis use leads to low striatal dopamine synthesis and release, and there is much evidence that these low dopamine levels drive craving for further drug use (Bloomfield et al., 2014; Murray et al., 2014). Antipsychotics block dopamine and therefore may compound this low striatal dopamine leading to greater craving as well as anhedonia, and consequent unwillingness to take further antipsychotics.

It is unclear whether stopping smoking or cannabis use would mitigate the increased liability of poor medication adherence and non-remission showed by patients continuing to smoke or use cannabis after their psychosis onset. However, some hope comes from the finding that premorbidly

nicotine dependent and cannabis using patients were not differentiable from never smokers and cannabis-naïve subjects in terms of medication adherence and odds of remission. In contrast, our results show that nicotine dependence and cannabis use after psychosis onset are associated with a higher probability of having non-remission from a first episode of psychosis and should be treated as risk factors for poor medication adherence and subsequent poor clinical outcome. Furthermore, nicotine dependence and cannabis use have been shown to greatly elevate odds of having a poor general health in later life among psychosis patients. In particular, smoking is 2 to 3 times more frequent in psychosis patients compared to healthy subjects and is considered to contribute significantly to the elevated rates of cardiovascular morbidity and mortality among patients with psychosis (Depp et al., 2015). Similarly, a review of clinical studies has found cannabis use to impact negatively on a number of outcomes, including social functioning, physical health, rates and duration of hospitalization (Atakan, 2008). Thus, services caring for patients suffering their first episode of psychosis should invest resources in the treatment of their substance use to improve clinical outcomes and reduce subsequent burden on services.

4.1. Strengths and limitations

The main strengths of the present study are its prospective longitudinal design and its sample size. Moreover, it analyses all the most common used substances, both before and after psychosis onset. Instead, data collection methods at baseline and follow-up is a potential pitfall of the study, such that information collected at baseline was self-reported, while at follow-up, this information was obtained by clinical notes. This may have an impact on the comparability of these data. For example, self-report data may be more prone to recall bias even if it is less likely to occur when data are collected at the onset of the illness. Moreover, patients might be reluctant to disclose their substance use, though if true the latter would underestimate the magnitude of the effect reported. In contrast, the presence of multiple observers and multiple assessments at follow-up has ensured the reliability of data collected, also in light of the significantly high consistency amongst

the researchers involved in this study. Moreover, having patient clinical information stored electronically increases the availability of data, helping public health researchers to produce research that is beneficial to society and speeding the process of identifying evidence-based best practices. However, despite the benefits associated with using clinical records data for research, there are also great challenges. Because clinical records are designed to support health care provision, they are not structured in a way that facilitates the research process. In fact, providers can decide where to put information; information may be entered in free-text form instead of being entered in defined fields or picked from a structured list of medical terms; providers can use different terms for the same information (lack of standardization); information may not be stored in a way that is readily searchable and data that are not important to clinical care may be missing. Also, having only one short-midterm follow up point represents another limitation of this study. Finally, cannabis and tobacco are often consumed together in the same joint and there is accumulating evidence of a common underlying biological vulnerability to both substances (Agrawal et al., 2012). Even if this study aims statistically to assess the independent effect of each substance on both medication adherence and remission, further research is needed to definitively disentangle their independent contribution on patients' clinical outcome.

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